Docket #: S24-505

Predicting 3D Genome Architecture from Single-molecule Sequencing Data

Researchers at Stanford have developed FiberFold, a computational tool enabling the rapid analysis of 3D chromatin architecture in conjunction with chromatin accessibility, CTCF binding, CpG methylation, and underlying genetic architecture.

To gain a comprehensive understanding of the genomic regulatory landscape, it is essential to investigate various features underlying genomic regulation, such as CpG methylation, protein-DNA interactions, chromatin accessibility, and 3D genome structure. Previous methods have been developed to quantify these features individually, but they can be costly, time-consuming, and have technical shortcomings intrinsic to short-read sequencing approaches. These methods are also limited in their ability to resolve individual haplotypes, repetitive genomic regions, and the combinatorial interactions between regulatory machinery.

Stage of Development
Research: in vitro

Stage of Research
The inventors have developed a computational method called FiberFold that builds on on recent advancements in genomic machine learning and single-molecule sequencing to predict 3D chromatin architecture while simultaneously assaying genetic variation, chromatin accessibility, and CpG methylation state.

Applications

- FiberFold can
    - be used to predict 3D genomic contacts in a de novo, cell-line-specific manner.

    - increase the utility of single-molecule sequencing.
    - determine 3D topologies of the active versus inactive X chromosome, showing haplotype-specific chromosome accessibility.

Advantages

- FiberFold is the first method capable of measuring 3D chromatin architecture in conjunction with chromatin accessibility, CTCF binding, CpG methylation, and underlying genetic architecture in one assay, thus increasing the utility of single-molecule sequencing.
- FiberFold can be trained on data from a single cell type and can successfully generalize to other cell types.

Publications

- Dubocanin, D. Altemose, N., et al.. Resolving Haplotype-specific 3D Chromatin Organization by Integrating Deep Learning with Single-Molecule Sequencing, *in press*.

Patents

- Published Application: WO2026169727

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